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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte TIMOTHY J. BARBERICH,
PAUL D. RUBIN and WILLIAM E. YELLE

Appeal No. 2005-0906
Application No. 09/527,844

HEARD: July 12, 2005

Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-15 and 50-53. Claims 1 and 5 are representative of the subject matter on appeal, and read as follows:

1. A method of treating or prophylaxis of a disorder ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors in a patient which comprises administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

5. The method of claim 1 wherein the ziprasidone metabolite is ziprasidone sulfoxide or ziprasidone sulfone.

The examiner relies upon the following references:

Lowe, III et al. (Lowe)	4,831,031	May 16, 1989
Allen et al. (Allen)	5,312,925	May 17, 1994

Davis et al. (Davis), "Ziprasidone," CAPlus Abstract, Copyright 2002, American Chemical Society, referencing CNS Drugs, Vol. 8, No. 2, pp. 153-159 (1997).

Prakash et al. (Prakash), "Metabolism and Excretion of a new Antipsychotic Drug, Ziprasidone, in Humans," Drug Metabolism and Disposition, Vol. 25, No. 7, pp. 863-869 (1997).

Claims 1-4 and 6-9 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Davis. In addition, claims 1-15 and 50-53 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Davis, Lowe, Allen and Prakash. After careful review of the record and consideration of the issues before us, we reverse both rejections of record.

BACKGROUND

Ziprasidone is a highly potent 5-HT_2 and dopamine D_2 receptor antagonist, and while characterized as an antipsychotic, it may also have anxiolytic and antidepressant effects due to ability to inhibit serotonin and noradrenaline uptake. See Specification, page 1. According to the specification, at least twelve metabolites of ziprasidone have been identified in humans, but ~~that~~ the prior art has reported that the metabolites are not active at the D_2 and 5-HT_{2A} receptor sites. See id. at 1-2.

The specification teaches further that "Ziprasidone offers a number of benefits, but unfortunately many adverse effects are associated with its administration. Examples of adverse affects of ziprasidone include, but are not

limited to, nausea, somnolence, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances, male sexual dysfunction, and elevated serum liver enzyme levels. . . . It is thus desirable to find a compound which possesses advantages of ziprasidone but fewer of its disadvantages." Id. at 2-3.

Thus,

> [t]his invention relates to novel methods using, and compositions comprising, ziprasidone metabolites, preferably, ziprasidone sulfoxide and ziprasidone sulfone. These metabolites, prior to the present invention, have been reported to have little or no in vivo activity. The present invention encompasses the in vivo use of these metabolites, and their incorporation into pharmaceutical compositions and single unit dosage forms useful in the treatment and prevention of disorders that are ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors. Such disorders include psychotic and neuroleptic disorders. In a preferred embodiment, ziprasidone metabolites are used in the treatment or prevention of neuroleptic and related disorders in mammals, including humans.

Id. at 3.

The specification describes pharmaceutical compositions comprising ziprasidone metabolites, see id. at 7, as well as methods of preparing the sulfoxide and sulfone metabolites, see id. at 7-8.

DISCUSSION

The issues in this case turn primarily on claim construction—specifically the construction of the term "administering" in the claims.

According to the examiner, the term "administering" should be construed as encompassing the administration of the parent drug, ziprasidone, "because metabolites of ziprasidone are necessarily and inevitably formed under normal

condition[s] [sic] once ziprasidone is administered to a patient." Examiner's Answer, page 7.

Appellants argue that the examiner's construction of the term "administering" is contrary to its ordinary meaning. See Appeal Brief, page 10. Appellants argue that "administering" refers to "a compound that exists outside of the patient [which] is given, or applied to the patient." Id. Appellants argue further that the examiner's construction is contrary to unambiguous statements made during prosecution "that the term 'administration' or 'administering,' as used in the claims, means giving to a patient a compound as it exists outside of the body." Id. at 13.

During ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification as it would be interpreted by the ordinary artisan. See Phillips v. AWH Corp., 2005 WL 1620331, *9 (Fed. Cir.) (en banc) (citing In re Am. Acad. Of Sci. Tech. Ctr., 367 F.3d 1359, 1364 (Fed. Cir. 2004). Thus, it is "entirely appropriate . . . when conducting claim construction to rely heavily on the written description for guidance as to the meaning of the claims." Id.

In the case before us, the specification focuses entirely on the preparation of ziprasidone metabolites, teaching their synthesis and their incorporation into pharmaceutical compositions. Thus, we construe "administering" as used in the claims as requiring the ex vivo preparation of the ziprasidone metabolite, which

is then given to the patient, and excluding giving the patient the parent drug ziprasidone.

Claims 1-4 and 6-9 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Davis.[1]

According to the rejection:

> Davis [ ] discloses ziprasidone as an antipsychotic drug having high affinity for serotonin 5-Ht2 and dopamine D2 receptors. Davis [ ] also discloses administration of this drug to patients. Davis further indicates that clinical trials have shown ziprasidone to be effective in treating depression associated with schizophrenia and in reducing anxiety in patients about to undergo dental surgery.

Examiner's Answer, page 3.

It is axiomatic that in order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. See In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). As we have construed "administering" as requiring ex vivo preparation of the ziprasidone metabolite, which is then given to the patient, the Davis abstract does not anticipate the claim, as it does not

[1] We note that the examiner relies solely on the abstract of the Davis article, and from our review of the record, it does not appear that the entire reference has been made of record. "Citation of and reliance upon an abstract is generally inappropriate where both the abstract and the underlying document are prior art." MPEP §706.02 (II) (8th edition, Revision 2, May 2004). Moreover, in order for meaningful appellate review to occur, the examiner must present a full and reasoned explanation of the rejection see, e.g., In re Lee, 277 F.3d 1338, 1342, 61 USPQ2d 1430, 1432 (Fed. Cir. 2002), and that would include analysis of the full underlying document.

teach or suggest the use of metabolites of ziprasidone in that manner. The rejection of claims 1-4 and 6-9 under 35 U.S.C. § 102(b) as being anticipated by Davis is thus reversed.

The examiner asserts that the administration of metabolites of ziprasidone is inherent in the administration of the parent drug, ziprasidone. See Examiner's Answer, page 6. The examiner cites Zenith Laboratories, Inc. v. Bristol Myers Squibb, Co., 19 F.3d 1418, 30 USPQ2d 1285 (Fed. Cir. 1994) in support of that assertion, arguing that case "provides that ziprasidone metabolites are necessarily and inevitably formed from the ziprasidone under normal condition[s] [sic]." Id.

We do not disagree that ziprasidone metabolites are "necessarily and inevitably formed" upon the administration of ziprasidone. Claim 1, however, as construed by the panel, requires the ex vivo preparation of the ziprasidone metabolite, which is then given to the patient. That limitation is neither taught nor suggested by the Davis abstract, and thus the Davis reference does not teach the method of claim 1. The court's decision in Zenith Laboratories is not on point, as the claim at issue in that case was drawn to a compound, and the court construed the claimed compound as not being limited to the compound in its preingested form. See id. 19 F.3d at 1422, 30 USPQ2d at 1288. Thus, the decision in that case, as in the case before us, turned on the construction of the claim, and we have construed the claim to exclude giving the patient the parent drug, ziprasidone.

The examiner argues further that instant claim 1 is analogous to a product-by-process claim, as "the product employed in a method claim[ ] may not be limited to the manipulations of the steps creating the product, only the structure implied by the steps, here, ziprasidone metabolites." Examiner's Answer, page 8. According to the examiner, as the patentability of a product does not depend on its method of production, it is irrelevant to the patentability of the claim whether the ziprasidone metabolite is synthesized ex vivo or produced through the metabolism of the parent drug. See Examiner's Answer, pages 8-9.

We do not find the examiner's reasoning to be persuasive. The claims at issue, such as claim 1, are not product-by-process claims. The claim as construed here requires the ex vivo preparation of the ziprasidone metabolite, which is then given to the patient, and as noted above, the Davis abstract does not teach or suggest giving a ziprasidone metabolite, which has been prepared ex vivo, to a patient.

We note that both the examiner and appellants argue that the holding in Schering Corp. v. Geneva Pharmaceuticals, Inc., 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003) supports their position. In that case, the court held that claims drawn to a loratadine metabolite, DCL, were inherently anticipated by prior art drawn to the administration of loratadine, as "DCL necessarily and inevitably forms from loratadine under normal conditions." Id., 339 F.3d at 1378, 67 USPQ2d at 1668. That holding is distinguishable from the case before us

because the claims are not drawn to the metabolite per se, but to a method of administering the metabolite, which we have construed as requiring ex vivo preparation of the metabolite, which is then given to the patient.

In addition, appellants rely on the following language from Schering. See Appeal Brief, page 11.

> Finally, this court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs. With proper claiming, patent protection is available for metabolites of known drugs. . . .
>
> * * *
>
> A skilled patent drafter, however, might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, as in *Kratz* and *Bergstrom*, or as a pharmaceutically composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The '233 patent would not provide an enabling disclosure to anticipate such claims because, for instance, the '233 patent does not disclose isolation of DCL.

Id., 339 F.3d at 1378, 67 USPQ2d at 1670.

We note that as we need not rely on the above passage from Schering in reaching our decision today, based on our construction of "administering," we decline to address the argument of whether the above passage is dictum, as argued by the examiner, or necessary to the holding in Schering, as argued by appellants.

Claims 1-15 and 50-53 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Davis, Lowe, Allen and Prakash.

Davis is relied upon as above. The examiner states that "Davis does not specifically teach metabolites of ziprasidone, the amounts (i.e., dosage), or routes of administration as instantly claimed." Examiner's Answer, page 4.

Lowe is relied upon for teaching that ziprasidone and ~~their~~ its pharmaceutically acceptable salts may be administered orally, in the form of tablets or capsules, or parentally. Allen is relied upon for teaching the use of ziprasidone hydrochloride as a neuroleptic agent. See id.

Prakash is cited for teaching the affinity of the sulfone and sulfoxide metabolites of ziprasidone for 5HT2 and D2 receptors. See id.

The rejection concludes:

> It would have been obvious to one of ordinary skill in the art at the time of the invention to employ ziprasidone or any of its known salts or metabolites, including the sulfone and sulfoxides, in a method for treating neuroleptic disorders.
>
> One of ordinary skill in the art would have been motivated to employ ziprasidone or any of its known salts or metabolites in a method of treating neuroleptic disorders, because ziprasidone and ziprasidone hydrochloride are known in treating anxiety, depression associated with schizophrenia and situational anxiety (i.e. anxiety prior to dental surgery). Further, employment of different salts and metabolites of a known active, as an alternative form of different salts and metabolites of a known active, as an alternative form of drug delivery, is within the skill of the artisan and therefore obvious.

Id. at 4-5.

"[T]he Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to

combine the relevant teachings of the references.'" In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citation omitted). An adequate showing of motivation to combine requires "evidence that 'a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.'" Ecolochem, Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1076 (Fed. Cir. 2000).

As argued by appellants, see Appeal Brief, page 16, Prakash teaches that "[t]he affinities of the sulfoxide and sulfone metabolites for 5-HT_2 and D_2 receptors are low with respect to ziprasidone, and are thus unlikely to contribute to its antipsychotic effects." Prakash, abstract. Thus, the skilled artisan would not have been motivated to substitute the sulfoxide and sulfone metabolites for the ziprasidone parent drug in the methods of Davis, Lowe and Allen. The examiner has therefore not established a prima facie case of obviousness, and the rejection of claims 1-15 and 50-53 under 35 U.S.C. § 103(a) is reversed.

The examiner argues that "Prakash teaches that sulfone or sulfoxide metabolites are major metabolites of ziprasidone . . . and that they possess agonistic affinities towards 5HT2 and D2 receptors. Such agonistic properties would have motivated the skilled artisan to employ sulfone or sulfoxide metabolites in a therapeutic regimen absent information to the contrary." Examiner's Answer, page 11. Moreover, according to the examiner, the fact that "sulfone or sulfoxide metabolites have low affinities towards their receptors is not

persuasive, because such [a] [sic] statement is not an indication that they are void of any value for the same therapeutic purpose as ziprasidone." Id. at 12.

The examiner's argument begs the issue, that is, whether a person of ordinary skill in the art would have been motivated to combine the references to arrive at the claimed invention. Obviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art. See In re Kuderna, 426 F.2d 385, 389, 165 USPQ 575, 578 (CCPA 1970); see also In re Shuman, 361 F.2d 1008, 1012, 150 USPQ 54, 57 (CCPA 1966). In assessing the teachings of the prior art references, the examiner should also consider those disclosures that may teach away from the invention. See In re Geisler, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997). As discussed above, Prakash, although arguably teaching that the sulfone and sulfoxide metabolites have some affinity for the 5-HT_2 and D_2 receptors, specifically teaches that the affinities are low as compared to ziprasidone, and are thus unlikely to contribute to its antipsychotic effects, and thus Prakash would not motivate the ordinary artisan to substitute ziprasidone metabolites for ziprasidone in the method taught by the other references.

CONCLUSION

Based on our construction of "administering" as used in the claims at issue, we reverse the rejection of claims 1-4 and 6-9 under 35 U.S.C. § 102(b) as being anticipated by Davis. Moreover, we also reverse the rejection of claims 1-15 and 50-53 under 35 U.S.C. § 103(a) as being obvious over the combination of Davis, Lowe, Allen and Prakash, as the examiner failed to set forth a prima facie case of obviousness.

REVERSED

Demetra J. Mills)
Administrative Patent Judge)
)
)
Eric Grimes) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
Lora M. Green) INTERFERENCES
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